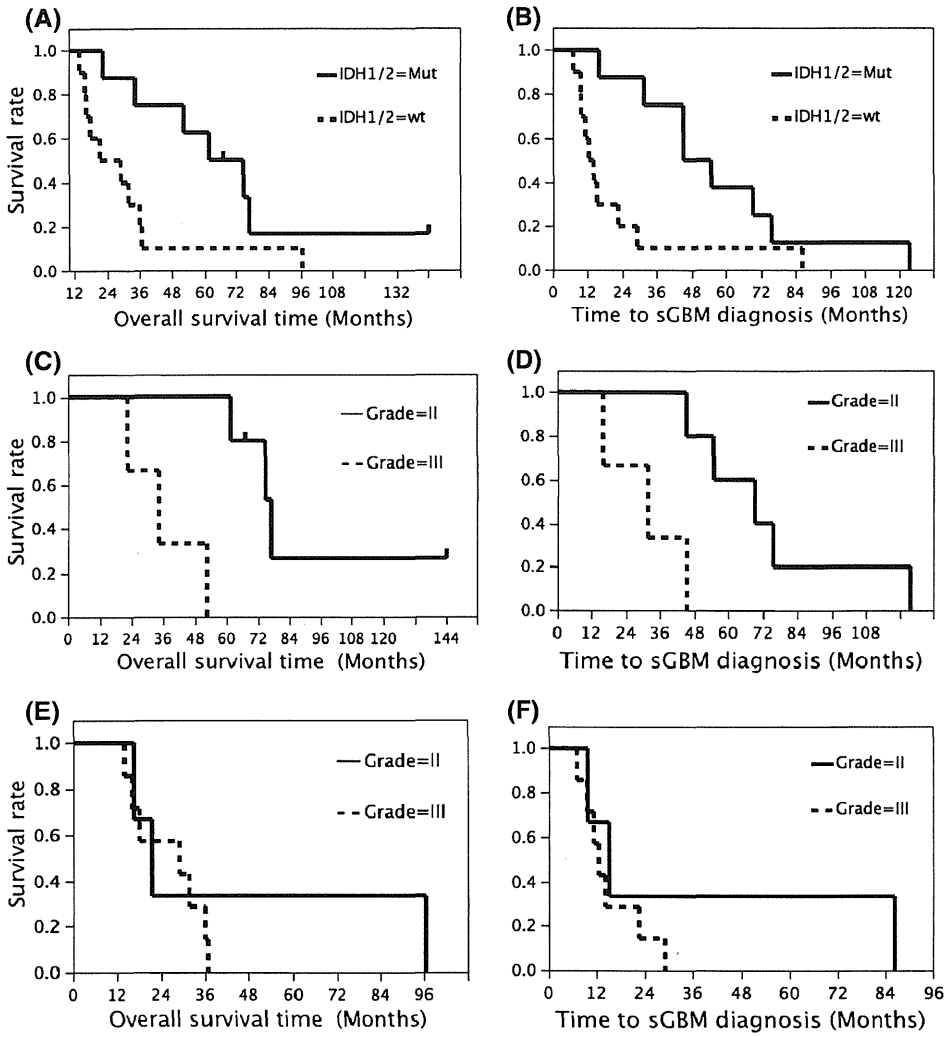

Fig. 1 Kaplan–Meier curves of overall survival time and time to the diagnosis of secondary glioblastoma (sGBM) in patients with *IDH1/2* wild-type and mutated tumors according to the initial tumor grades. **a** The median overall survival time was 68.2 months in patients with sGBM-Mut and 25.3 months in those with sGBM-Wt ($p = 0.029$). **b** The median time to sGBM diagnosis was 50.1 months in patients with sGBM-Mut and 13.4 months in those with sGBM-Wt ($p = 0.021$). **c** In patients with sGBM-Mut, the median overall survival time was 76.9 months for initial grade II tumors and 34.2 months for initial grade III tumors ($p = 0.0042$). **d** In patients with sGBM-Mut, the median time to the diagnosis of sGBM from initial grade II tumors was 69.3 and 31.7 months from initial grade III tumors ($p = 0.022$). **e** In patients with sGBM-Wt, the median overall survival time was 21.5 months for initial grade II tumors and 29 months for initial grade III tumors ($p = 0.51$). **f** In patients with sGBM-Wt, the median time to the diagnosis of sGBM was 15.2 months from initial grade II tumors and 12.6 months from initial grade III tumors ($p = 0.34$)

the remaining one-third of sGBM-Wt had neither *TP53* mutations nor 1p/19q codeletion.

IDH1/2 mutations are reported to be observed in 46–88 % of sGBMs [3–5, 7, 9, 25, 26]. In our study, 44.4 % (8 of 18) of sGBMs had *IDH1/2* mutations, which seems to be less frequent. However, Mukasa et al. [25] reported the frequency of *IDH1/2* mutations was observed 46 % (6 of 13) of sGBM, and Ichimura et al. [5] reported 50 % (5 of 10). These reports are comparable to our observations. The possible reason of the relatively low frequency of *IDH1/2* mutations in our cases is likely due to the different patients cohort. Patients cohorts may be different in the age, the number of patients, and the proportion of initial grade II/III tumor ratio. Selection criteria of sGBM may be different: some reports exclude patients whose preceding lower-grade glioma were diagnosed <1 year prior to the sGBM diagnosis [7]. These factors may influence on the frequency of *IDH1/2* mutations of sGBM.

In our result, the overall survival time and the time from initial diagnosis to sGBM diagnosis were significantly shorter in patients with sGBM-Wt than in those with

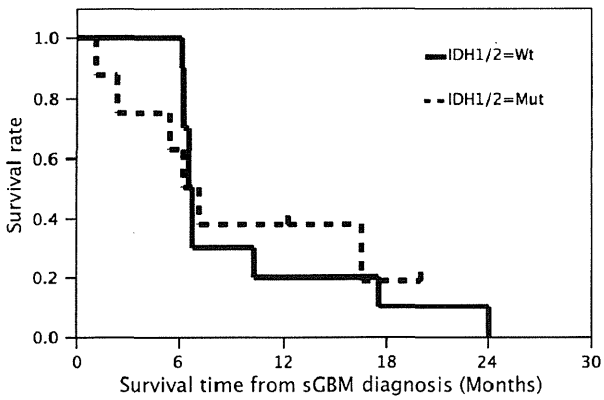

Fig. 2 Kaplan–Meier survival curves from the diagnosis of secondary glioblastoma (sGBM) according to the *IDH1/2* mutation status. The median survival time from the diagnosis of sGBM was not different between the patients with wild-type and mutant *IDH1/2* (6.8 vs. 6.75 months, $p = 0.93$)

Table 3 Summary of genetic alterations of secondary glioblastomas with wild-type or mutant *IDH1/2*

	sGBM-Wt ($n = 9$)	sGBM-Mut ($n = 7$)	p
TP53 mutations			
Yes	6	7	0.046*
No	3	0	
1p/19q codeletion			
Yes	0	0	
No	9	7	
CDKN2A homozygous deletion			
Yes	2	3	0.38
No	7	4	
PTEN deletion			
Yes	2	1	0.68
No	7	6	
EGFR amplification			
Yes	2	0	0.11
No	7	7	

sGBM secondary glioblastoma, *IDH* isocitrate dehydrogenase, *sGBM-Wt* secondary glioblastoma with wild-type *IDH1/2*, *sGBM-Mut* secondary glioblastoma with *IDH1/2* mutation, *CDKN2A* cyclin-dependent kinase inhibitor 2A, *PTEN* phosphatase and tensin homologue, *EGFR* epidermal growth factor receptor

* Statistically significant

sGBM-Mut. Moreover, in patients with sGBM-Mut, the time to sGBM diagnosis was significantly longer from initial grade II diagnosis than from initial grade III diagnosis. This difference is consistent with the previous reports [1]. However, in patients with sGBM-Wt, it was much shorter from initial grade II diagnosis, and more importantly, it was not different between from initial grade II and III diagnosis. Although the number of patients in this study was not sufficiently large enough to draw a definite conclusion, this rapid progression to sGBM-Wt leads us to the need for the intense treatment to the lower-grade gliomas if they do not carry have *IDH1/2* mutations.

The median survival of patients from the diagnosis of sGBM was not found to vary between the wild-type and mutant *IDH1/2* (6.8 vs. 6.75 months, $p = 0.93$). This survival time from the sGBM diagnosis is comparable to previous reports that report a median survival time of 0.6 years for patients diagnosed as initial low-grade glioma and GBM on recurrence [27]. However, recently, SongTao et al. [19] reported that 86 patients with sGBM treated with TMZ who did not have previous chemotherapy and that patients with *IDH1/2* mutated sGBM had longer survival time and better response to TMZ than those with *IDH1/2* wild-type sGBM. This report showed the predictive value of *IDH* mutation in patients with sGBM treated with TMZ, suggesting the possibility that *IDH1/2* mutations have an impact on the clinical course after sGBM.

In our analysis, sGBM-Mut tended to be associated with younger age and a higher frequency of predominant frontal location than sGBM-Wt. These results are in agreement with the previous reports on both sGBMs and pGBMs [16, 19]. These differences may also influence the difference in clinical course of tumors with and without *IDH1/2* mutations, as reflected by their overall survival time and time to the diagnosis of sGBM.

Our genetic analysis shows that all sGBM-Mut have *TP53* mutations but none had *EGFR* amplification. This finding corroborates with the previous reports where *IDH1/2* mutations have been associated with *TP53* mutations [2]. Watanabe et al. [6] did not observe a single case in which an *IDH1* mutation occurred after the acquisition of a *TP53* mutation from analyses of paired initial and recurrent tumors, suggesting that *IDH1* mutation is the earliest genetic changes and that the additional acquisition of *TP53* mutations may lead to astrocytic differentiation. This hypothesis suggests that the alteration of the *TP53* pathway may play a crucial role in progression from precursor cells carrying *IDH1/2* mutations into astrocytic tumors [28].

Compared with sGBM-Mut, the genetic alterations of sGBM-Wt were more heterogeneous. In our series, 66.7 % (6 of 9) of sGBM-Wt harbored *TP53* mutations. Based on the reports that 20–30 % of clinically defined pGBMs with wild-type *IDH1/2* have *TP53* mutations [7, 9], *TP53* mutations are also considered to be an important genetic alterations in *IDH*-independent pathway. One of the sGBMs-Wt with *TP53* mutations (DA 065) had *EGFR* amplification, and the other (AO004) had *PTEN* deletion, suggesting that the PI3K/AKT pathway also plays an important role in these tumors. We encountered 3 sGBM-Wt that did not have alterations in *TP53*, or 1p/19q. These

"triple negative" tumors account for approximately 7 % of low-grade gliomas [29], in which RB1 pathway alteration is a common genetic event [30]. One of the "triple negative" sGBMs (AA043) had *EGFR* amplification, *PTEN* deletion, and *CDKN2A* homozygous deletion, which was similar to the classic glioblastomas of The Cancer Genome Atlas classification [31]. This suggests that a part of "triple negative" sGBMs exhibit a genetic pattern similar to that of pGBMs. Further, 2 of the tumors (AA017 and AOA010) did not contain any genetic alterations among those examined.

It has been suggested that the clinically defined sGBM-Wt might actually be pGBM, where higher-grade histology was not presented in the submitted specimen due to undersampling [9]. This suggestion was based on the findings that sGBM with wild-type *IDH1* have infrequent *TP53* mutations (20 %), and most preceding lower-grade gliomas consisted of grade III tumors [9]. However, this explanation does not account for all cases. Most patients (8 of 10) with wild-type *IDH1/2* gliomas had more than partial surgical resection at initial operation, which minimizes the possibility of misclassification due to undersampling, although extensive surgical resection does not always guarantee appropriate sampling. Moreover, in our series 66.7 % of sGBM-Wt harbored *TP53* mutations, which were more frequent than previous report [9]. In fact, Shibahara et al. [32] experienced grade II or III gliomas without *IDH1* mutations progressed to sGBM without *IDH1* mutations. Based on these considerations, at least some sGBMs with wild-type *IDH1/2* might actually develop in a stepwise fashion from lower-grade gliomas through *IDH*-independent pathway.

In summary, our observations suggest that *IDH1/2* mutations have an impact on the glioma history of sGBM with different genetic pathway. The aggressive progression to sGBM-Wt suggests the need for more intense treatment to the *IDH1/2* wild-type tumors.

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Conflict of interest The authors declare that they have no conflict of interest.

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Secondary hematological malignancies associated with temozolomide in patients with glioma

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Background. The alkylating agent temozolomide (TMZ) is widely used for the treatment of gliomas. Although reports of treatment-related myelodysplastic syndrome (MDS), acute myeloid leukemia (AML), and acute lymphoblastic leukemia (ALL) associated with TMZ are accumulating, it remains unclear whether TMZ has the same leukemogenic potential as other alkylating agents.

Methods. We performed a single-institution retrospective analysis using a database of 359 glioma patients given nimustine (ACNU)-based therapy, TMZ-based therapy, or combination therapy, who were followed up for a minimum of 2 months, between January 1990 and December 2009, at the National Cancer Center Hospital in Japan.

Results. Of the 359 patients, 225 received ACNU alone or ACNU plus other chemotherapeutic drugs (ACNU-based group; median follow-up period, 31.4 mo), 63 patients received ACNU-based therapy followed by TMZ therapy (ACNU-TMZ group; median follow-up period, 19.1 mo), and 71 patients received TMZ alone or TMZ plus other chemotherapeutic drugs (TMZ-based group; median follow-up period, 16.9 mo). Three patients in the ACNU-based group developed MDS/AML (incidence rate: 2.9 cases per 1000 person-years), 2 patients in the ACNU-TMZ group developed MDS/AML (13.0 cases per 1000 person-years), and 1 patient in the TMZ-based group developed ALL (9.9 cases per 1000 person-years).

Conclusions. Despite the limitations of this study, published reports and our results suggest that TMZ induces secondary hematological malignancies, particularly ALL, and might shorten the latency period when used in combination with other chemotherapeutic agents.

Keywords: alkylating agent, glioma, secondary hematological malignancy, temozolomide.

Gliomas are the most common malignant primary brain tumors, consisting mainly of astrocytic, oligodendroglial, and oligoastrocytic tumors. Malignant gliomas that represent World Health Organization (WHO) grades III and IV tumors form one of the most malignant and devastating groups of human cancers.[1] Malignant gliomas are intractable to combination therapy with surgical resection, radiation, and chemo, and their prognosis remains dismal, with a poor median survival.[2] Although a number of chemotherapies had been tested and several chemotherapeutic agents, such as nitrosoureas, demonstrated significant effect for the treatment of gliomas,[3–6] there was no standard chemotherapy regimen until temozolomide (TMZ) was introduced into clinical practice.[7]

TMZ is an oral alkylating agent, and its efficacy was initially tested and demonstrated in the treatment of glioblastoma. The antitumor effect of TMZ was observed when combined with radiotherapy in patients with glioblastoma.[7] Following the demonstration of prolonged survival in glioblastoma patients treated with TMZ compared with patients receiving radiotherapy alone (14.6 mo vs 12.1 mo),[7] TMZ became the most widely used chemotherapeutic agent for various types of gliomas.[2] Although the mechanism of action of TMZ is similar to that of other alkylators, TMZ causes side effects such as lymphocytopenia.[8] Although the long-term side effects of TMZ are still uncertain, reports of treatment-related myelodysplastic syndrome (MDS) and leukemia associated with TMZ are accumulating.[9–16]

Cancer survivors are at a substantially higher risk for developing additional cancers than the general

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population, and this risk for secondary malignancy should be noted by health care professionals.[17] Alkylating agents are generally known as leukemogenic drugs, and their potential for causing cancers is higher than that of other chemotherapeutic agents.[17–19] Before the TMZ era, the alkylator nimustine (ACNU) was predominantly used for the treatment of malignant gliomas in Japan, and we encountered several cases of secondary MDS and acute myeloid leukemia (AML) after ACNU-based chemotherapy. Since TMZ became available in Japan in September 2006, we switched the first-line chemotherapeutic agent from ACNU to TMZ for newly diagnosed malignant gliomas and recurrent gliomas. After sequential use of TMZ following ACNU, we encountered additional cases of secondary MDS/AML. However, it remains unclear whether TMZ has the same leukemogenic potential as other alkylating agents. To characterize secondary hematological malignancies and to estimate the rate of MDS and leukemias associated with TMZ-based therapy compared with ACNU-based therapy, we reviewed 359 glioma patients receiving ACNU and/or TMZ-containing chemotherapy.

Patients and Methods

Study Population and Therapeutic Management

The study population consisted of 359 consecutive glioma patients of Japanese origin who had received chemotherapy at the National Cancer Center Hospital, Tokyo, Japan from 1990 to 2009. All patients were diagnosed with glioma of WHO grades I to IV either pathologically (in most cases) or radiographically (in cases of brainstem tumors) and were treated with one of the following: (i) ACNU-based therapy: ACNU alone or ACNU plus other chemotherapeutic drugs; (ii) TMZ-based therapy: TMZ alone or TMZ plus other chemotherapeutic drugs; or (iii) ACNU-TMZ therapy: ACNU-based therapy followed by TMZ-based therapy. In the TMZ-based group, TMZ was continued for 24 cycles or until the tumor disappeared. The patients in all 3 groups were followed up for a minimum of 2 months. Secondary hematological malignancies were diagnosed by bone marrow aspiration either by a pediatric oncologist or by a hematologist. Local brain radiotherapy was performed in most patients within 2 weeks after the operation, using a dose of 54 Gy in patients with WHO grade II gliomas or 60 Gy with a local boost in patients with WHO grades III and IV gliomas. To estimate the actual time at risk, person-years (the total sum of the number of years that each patient of a population had been under observation) and the incidence rate per 1000 person-years were calculated.

Statistical Analysis

Comparison between 2 groups was performed using Student's *t*-test. Correlations between 2 groups were assessed using a chi-square test. The analyses were performed using JMP7 version 7.0.1 software (SAS Institute). $P < .05$ was considered statistically significant.

Results

Patient Characteristics and Clinical Outcome

The patient demographics and follow-up periods in the 3 treatment groups are shown in Table 1. Of the 359 patients included in the study, 210 were men and 149 were women. The median age was 47 years (range, 0–80 y), and the median follow-up time was 22.0 months (range, 2.2–232.6 mo). Because TMZ was introduced in Japan when ACNU was the first-line therapy for glioma patients, the numbers of patients were smaller and the follow-up periods were shorter in the ACNU-TMZ and TMZ-based groups than in the ACNU-based group. Pathological or radiographical diagnosis and WHO grade of the tumors at the start of treatment are shown in Table 2. The most frequent tumor type was glioblastoma (37.3%), followed by anaplastic astrocytoma (18.1%) and diffuse astrocytoma (18.1%). High-grade gliomas of WHO grades III and IV accounted for 66.5% of the tumors.

Treatment, Follow-up Period, and Hematological Malignancy

The chemotherapeutic drugs used in the patients and the related hematological malignancies are summarized in Table 3. In the ACNU-based group, 72 of 225 patients were treated with ACNU alone, and the other patients received a combination chemotherapy such as ACNU + etoposide (VP-16), ACNU + vincristine (VCR), or procarbazine (PCZ) + ACNU + VP-16. Because the patients with recurrence received second-line or third-line therapy, the number of chemotherapeutic drugs used was higher in cases with recurrence. In the ACNU-TMZ group, all 63 patients received ACNU-based therapy as first line, and TMZ was administered at recurrence. In the TMZ-based group, all 71 patients were treated with TMZ according to the regimen previously reported,[3] and in patients with recurrent tumors, either TMZ + PCZ or carboplatin + VP-16 therapy was sequentially administered. The median follow-up time was longer ($P < .001$) and the percentage of 2-year survivors was higher ($P < .001$) in the ACNU-based group than in the other groups treated with TMZ for the abovementioned reason. The median duration of TMZ therapy was 19.9 months (range, 1.0–51.5 mo) in the ACNU-TMZ group and 17.0 months (range, 2.5–24.5 mo) in the TMZ-based group.

Hematological malignancies were observed during or after chemotherapy in 6 patients. In the ACNU-based group, all 3 MDS/AML patients were treated with ACNU + VP-16. In the ACNU-TMZ group, 2 patients developed MDS/AML after ACNU followed by TMZ

Table 1. Patient characteristics and treatment

	ACNU-based	ACNU-TMZ	TMZ-based	Total
n (%)	225 (62.7)	63 (17)	71 (19.8)	359 (100)
Sex ratio (M/F)	1.45 (133/92)	1.42 (37/26)	1.29 (40/31)	1.41 (210/149)
Median age, y (range)	45.0 (0–77)	48.0 (19–66)	58.0 (12–80)	47.0 (0–80)
Median follow-up, mo (range)	31.4 (2.2–232.6)	19.1 (2.3–227.4)	16.9 (2.5–37.4)	22.0 (2.2–232.6)

Table 2. Pathological diagnosis and treatment

n (%)	ACNU-based	ACNU-TMZ	TMZ-based	Total
Patients	225 (62.7)	63 (17.5)	71 (19.8)	359 (100)
Glioblastoma	75 (33.3)	19 (30.2)	40 (56.3)	134 (37.3)
Anaplastic astrocytoma	38 (16.9)	15 (23.8)	12 (16.9)	65 (18.1)
Anaplastic oligoastrocytoma	12 (5.3)	6 (9.5)	5 (7.0)	23 (6.4)
Anaplastic oligodendroglioma	9 (4.0)	2 (3.2)	2 (2.8)	13 (3.6)
Anaplastic ependymoma	0 (0.0)	0 (0.0)	1 (1.4)	1 (0.3)
Anaplastic ganglioglioma	0 (0.0)	0 (0.0)	2 (2.8)	2 (0.6)
Anaplastic glioneuronal tumor	0 (0.0)	1 (1.6)	0 (0.0)	1 (0.3)
Diffuse astrocytoma	42 (18.7)	18 (28.6)	5 (7.0)	65 (18.1)
Oligoastrocytoma	21 (9.3)	2 (3.2)	0 (0.0)	23 (6.4)
Oligodendroglioma	4 (1.8)	0 (0.0)	1 (1.4)	5 (1.4)
Pleomorphic xanthoastrocytoma	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.3)
Ependymoma	8 (3.6)	0 (0.0)	1 (1.4)	9 (2.5)
Ganglioglioma	2 (0.9)	0 (0.0)	0 (0.0)	2 (0.6)
Pilocytic astrocytoma	3 (1.3)	0 (0.0)	1 (1.4)	4 (1.1)
Myxopapillary ependymoma	0 (0.0)	0 (0.0)	1 (1.4)	1 (0.3)
Brainstem glioma	9 (4.0)	0 (0.0)	0 (0.0)	9 (2.5)
Unknown glioma	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.3)
WHO grade IV	75 (33.3)	19 (30.2)	40 (56.3)	134 (37.3)
WHO grade III	59 (26.2)	24 (38.1)	22 (31.0)	105 (29.2)
WHO grade II	76 (33.8)	20 (31.7)	7 (9.9)	103 (28.7)
WHO grade I	5 (2.2)	0 (0.0)	2 (2.8)	7 (1.9)
Unknown grade	10 (4.4)	0 (0.0)	0 (0.0)	10 (2.8)

or PCZ + ACNU + VP-16 followed by TMZ. In the TMZ-based group, 1 patient treated with TMZ alone developed acute lymphoblastic leukemia (ALL) as reported previously.[10] The incidences and mean person-years of hematological malignancies were 1.33% and 6.4 years, respectively, in the ACNU-based group, 3.17% and 2.4 years in the ACNU-TMZ group, and 1.41% and 1.1 years in the TMZ-based group, with no significant differences in the incidence between the groups. The incidence rates of hematological malignancies per 1000 person-years were 2.9 cases in the ACNU-based group, 13.0 cases in the ACNU-TMZ group, and 9.9 cases in the TMZ-based group, with no significant differences between the groups as well (Table 4). All of the 3 MDS/AML patients in the ACNU-based group were treated in combination with VP-16, and the incidence rate of this ACNU + VP-16 group was 6.1 cases per 1000 person-years. The 3 cases of secondary hematological malignancies after TMZ treatment are summarized in Table 5.

Discussion

In this report, we describe 6 cases of treatment-related hematological malignancies. Before the TMZ era, several other alkylating agents were used for glioma treatment. Among these alkylators, nitrosoureas such as carmustine (BCNU), lomustine (CCNU), and ACNU are known to be strong leukemogenic agents, and reports of treatment-related MDS (t-MDS) or acute leukemia (AL) in glioma patients treated with these nitrosoureas have accumulated.[9,20,21] In contrast, the alkylator TMZ has been approved for use only in the last decade, and its leukemogenic activity has not yet been fully evaluated. Although there are several reports of t-MDS/AL in association with TMZ, most of these patients were treated with TMZ after treatment with other alkylating agents.[9–11] To our knowledge, only 6 cases of t-MDS/AL have been reported to have occurred after chemotherapy with TMZ alone in glioma patients, including ours.[12–15,22] Interestingly, 4 out of 6 cases

Table 3. Treatment and hematological malignancy

Chemotherapy	Incidence of MDS/AL (%)	Hematological Malignancy	Median Follow-up, mo (range)	Two-Year Survivors (%)
ACNU-based	3/225 (1.33)		31.4 (2.2–232.6)	126/225 (56.0)
ACNU	0/72		38.6 (2.7–205.4)	46/72 (63.9)
ACNU, VP-16	3/35	MDS/AML	82.0 (2.2–228.5)	21/35 (60.0)
ACNU, VCR	0/24		68.6 (9.6–151.5)	20/24 (83.3)
ACNU, PCZ, VCR	0/18		55.2 (5.1–196.1)	17/18 (94.4)
ACNU, CBDCA, VP-16	0/29		18.2 (3.9–126.3)	11/29 (37.9)
ACNU, CDDP, VP-16	0/10		13.3 (6.5–109.5)	2/10 (20.0)
ACNU, PCZ, VCR, CBDCA, VP-16	0/3		31.4 (16.0–139.8)	2/3 (66.7)
ACNU, IFN, VP-16	0/4		13.3 (6.5–109.5)	3/4 (75.0)
ACNU, IFN, CDDP, VP-16	0/3		19.6 (9.1–53.9)	1/3 (33.3)
ACNU, CBDCA, VP-16, VCR	0/3		21.0 (17.7–36.3)	1/3 (33.3)
ACNU, VP-16, 5-FU	0/2		122.7 (14.5–230.9)	1/2 (50.0)
ACNU, IFO, VCR, CDDP, VP-16	0/2		16.4 (4.2–28.6)	1/2 (50.0)
ACNU, PCZ, VCR, CDDP, VP-16	0/2		36.1 (17.6–54.6)	1/2 (50.0)
ACNU, PCZ	0/2		14.2 (11.5–16.8)	0/2 (0.0)
ACNU, other drugs	0/16		19.25 (3.3–232.6)	4/16 (25.0)
ACNU-TMZ	2/63 (3.17)		19.1 (2.3–227.4)	27/63 (42.9)
ACNU, TMZ	1/21	MDS/AML	9.1 (2.3–76.6)	8/21 (38.1)
ACNU, CBDCA, VP-16, TMZ	0/9		8.2 (3.3–16.2)	0/9 (0.0)
ACNU, PCZ, TMZ	0/9		38.8 (5.5–76.0)	6/9 (66.7)
ACNU, VCR, TMZ	0/7		24.4 (3.9–48.9)	4/7 (57.1)
ACNU, PCZ, VCR, TMZ	1/6	MDS/AML	23.4 (4.8–227.4)	3/6 (50.0)
ACNU, PCZ, CBDCA, VP-16, TMZ	0/4		21.0 (19.1–35.3)	1/4 (25.0)
ACNU, other drugs, TMZ	0/7		51.8 (10.1–72.3)	5/7 (71.3)
TMZ-based	1/71 (1.41)		16.9 (2.5–37.4)	16/71 (22.5)
TMZ	1/59	ALL	16.6 (2.5–37.4)	12/59 (20.3)
TMZ, PCZ	0/10		19.1 (6.9–36.6)	3/10 (30.0)
TMZ, PCZ, CBDCA, VP-16	0/2		21.8 (19.1–24.5)	1/2 (50.0)

Abbreviations: CBDCA, carboplatin; CDDP, cisplatin; IFN, interferon-beta; 5-FU, 5-fluorouracil; IFO, ifosfamide.

Table 4. Incidence and person-years of hematological malignancies

Chemotherapy	Number of Patients	Mean Follow-up (y)	Number of MDS/AL	Incidence per Protocol (%)	Total P-Ys	Incidence per 1000 P-Ys (95% CI)
ACNU-based	225	4.53	3	1.3	1020	2.9 (1.0–8.6)
(ACNU, VP-16)	105	4.67	3	2.9	493	6.1 (2.1–17.7)
ACNU-TMZ	63	2.43	2	3.2	153	13.0 (3.6–46.4)
TMZ-based	71	1.41	1	1.4	101	9.9 (1.8–54.0)

Abbreviations: P-Ys, person-years; CI, confidence interval.

were ALL, suggesting that secondary hematological malignancy after single-agent chemotherapy with TMZ may manifest as ALL.[14,15]

Secondary leukemia in cancer survivors accounts for 5%–10% of all ALs.[23] Although secondary MDS/AML is the most frequent entity among patients with secondary leukemia, secondary ALL accounts for ~10% of all secondary leukemia cases.[23,24] The incidence of t-AL has been reported in a large prospective study of 1628 brain tumor patients treated with CCNU.[20] In that study, only 2 cases (0.12%) of t-AL were observed, but only 10.9% of the study participants

Table 5. Cases with secondary hematological malignancies after TMZ treatment

Age, y/ sex	Primary Tumor	ACNU-based Therapy	RT Dose (Gy)	TMZ Dose (mg/ m^2)	Latency After TMZ (mo)	Secondary Leukemia
58/M	DA	ACNU × 2	50.0	23 750	41	MDS/AML
64/M	DA	PAV × 4	50.0	8750	16	MDS/AML
12/F	AA	None	60.0	12 900	13	ALL

Abbreviations: DA, diffuse astrocytoma; RT, radiation therapy; PAV, procarbazine; ACNU, and etoposide (VP-16); AA, anaplastic astrocytoma.

were followed up for more than 2 years. Because the median latency between the initiation of therapy and the diagnosis of t-MDS/AML and ALL has been reported to be 31 months in brain tumor patients and 50–70 months in patients with other malignancies,[21,25,26] the incidence of t-AL may be much higher than reported. Chamberlain and Raizer[12] reported 7 cases of t-MDS/AML during the treatment of gliomas. Of the 7 patients, 5 were treated with nitrosoureas + TMZ and 2 were treated with TMZ alone. These data suggest that the combination of nitrosoureas and TMZ may increase the incidence of alkylator-induced MDS/AML and ALL. However, there are no data to indicate that TMZ is more likely to induce secondary hematological malignancies than nitrosoureas or to enhance the leukemogenic activity of other alkylators.

ACNU-based chemotherapy was predominant in Japan for the treatment of malignant gliomas until TMZ was introduced into clinical practice. The ACNU-based group represents the era of 1990–2004, and 3 patients with glioma in our facility presented with MDS/AML. Of note, all 3 patients with MDS/AML received combination therapy including ACNU and VP-16 with a relatively high incidence rate per 1000 person-years (6.1 cases), although the mean follow-up period in this group was longer than the others. Because VP-16 is also known to increase the risk for treatment-related hematological malignancies,[27,28] the combination of ACNU and VP-16 would have a higher leukemogenic risk. During the era when TMZ was used following ACNU-based therapy, we encountered 2 more patients with MDS/AML. Although the mean follow-up period was shorter in the ACNU-TMZ group than in the ACNU-based group (2.43 y vs 4.53 y), the incidence rate of MDS/AML per 1000 person-years was higher in the ACNU-TMZ group (13.0 cases vs 2.9 cases). Although data based on time of exposure are required to achieve a more accurate analysis, these results suggest that additional TMZ after ACNU-based therapy increases the risk and shortens the latency period of t-MDS/AML. In the TMZ-based group, the median follow-up period was too short to determine the leukemogenic potential of TMZ alone. However, as described previously, t-ALL is a potential secondary malignancy in patients who undergo TMZ treatment.[14,15]

In conclusion, our data and reported evidence indicate that TMZ may exhibit leukemogenic potential similar to other alkylating agents. The leukemogenic activity of TMZ may be manifested particularly when it is used sequentially after other alkylators. Because TMZ is a relatively new drug in clinical practice and can prolong survival in glioma patients, TMZ-related MDS/AML and ALL will become more frequent. Close follow-up of hematopoietic function is needed for patients treated with TMZ.

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Conflict of interest statement. The authors have no personal financial or institutional interest in any of the drugs or materials described in this article.

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The 70th Annual Meeting Special Topics — Part II: Multidisciplinary Treatment for High Grade Gliomas

Usefulness of Multimodal Examination and Intraoperative Magnetic Resonance Imaging System in Glioma Surgery

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Abstract

Extensive surgical removal of tumor tissue can contribute to longer survival for patients with gliomas. Intraoperative magnetic resonance (iMR) imaging is important for safe and maximal resection of brain tumors. A new operating room equipped with a 1.5-T MR imaging system and neuronavigation opened at Yamagata University Hospital in 2008. Using this new suite, we have safely treated over 200 cases. Use of iMR imaging improved glioma resection rates in 25 (34%) of 73 cases, and gross total resection was achieved in 48 patients (66%). Motor evoked potential (MEP) monitoring was performed in combination with iMR imaging for 32 gliomas. MEP monitoring was successful in 30 cases (94%). Transient decreases in MEP amplitude were seen in two patients. One patient showed transient motor weakness and another showed improvement of motor function. The iMR imaging system provides useful information for tumor resection that allows intraoperative modification of surgical strategies. Combining MEP monitoring with iMR imaging appears to offer the most effective method for safe glioma surgery near eloquent areas.

Key words: intraoperative magnetic resonance imaging, glioma, intraoperative monitoring

Introduction

Intraoperative magnetic resonance (iMR) imaging and neuronavigation have substantially changed the principles of surgery for brain tumors. iMR imaging can provide updated information on anatomical structures and unanticipated brain events, thereby allowing safer and more accurate surgery.[1-4] Our institution installed a fully integrated neurosurgical suite including neuronavigation and an intraoperative 1.5-T high-field MR imaging system (Surgical Suite®) in 2008. This system provides high-quality images with short scan times. The Surgical Suite® has separate components in the operating room and the MR imaging room, so can be used not only for intraoperative scanning, but also for pre- and postoperative scans and brain checks for inpatients at Yamagata University Hospital. Using this new suite, we have safely treated over 200 cases of brain tumors, including gliomas, metastatic brain tumors, meningiomas, and pituitary adenomas. This study reviews our initial experiences, to evaluate the advantages and limitations of this suite in glioma surgery.

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Material and Methods

Figure 1 shows the appearance of the operating system, Surgical Suite® (GE Healthcare, Milwaukee, Wisconsin, USA). The high-field (1.5-T) MR imaging system (Signa HDx; GE Healthcare) is located in a separate room, which allows us to use standard surgical instruments irrespective of their magnetic properties. Intraoperative MR imaging includes T_1-weighted, T_2-weighted, T_2^*-weighted, fluid-attenuated inversion recovery, diffusion-weighted, and T_1-weighted with gadolinium imaging. If necessary, diffusion tensor imaging can be performed. About 1 hour is needed for iMR imaging, including patient transfer time.

A total of 202 consecutive patients were treated in the Surgical Suite® at Yamagata University Hospital between July 2008 and September 2011. The histological diagnoses were glioma (n = 73, 36.1%), pituitary adenoma (n = 35, 17.3%), meningioma (n = 18, 8.9%), metastatic tumor (n = 19, 9.4%), and others (n = 57, 28.2%).

Surgical planning was based on multiple sequences of MR imaging performed 1 or 2 days before surgery. Using a navigation planning workstation (iPLAN 2.6; Brainlab AG, Feldkirchen, Germany), target lesions and important anatomical structures were coded as colored objects. Diffusion tensor imaging and functional MR imaging were performed to visualize important tract and functional areas (pyramidal tract, motor cortex, and speech area). If the tumor was located in or around the pyramidal tract and or motor cortex, electrophysiological monitoring such as motor evoked potential (MEP) monitoring was performed by transcortical stimulation using reduction to <50% amplitude compared to before tumor resection as the warning level. If the surgeon considered that the goals of surgery had been met or the risk of injury to a functional area or tract was high, iMR imaging was performed. If iMR imaging indicated incomplete resection, the surgical planning was revised according to the newly obtained images, and the surgical procedure was resumed based on the updated navigation information.

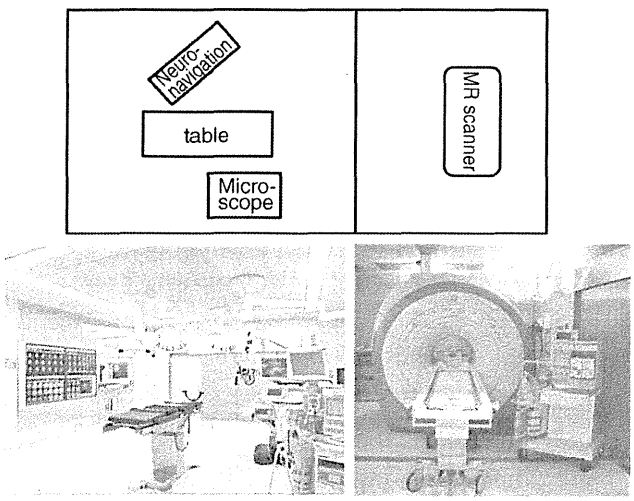

Fig. 1 Layout and photographs of the Surgical Suite®. A magnetically shielded sliding door separates the magnetic resonance (MR) imaging room (*right*) from the operation room (*left*).

The extent of resection (EOR) was determined by comparing the MR images obtained before surgery with those obtained within 72 hours after surgery. EOR was calculated based on manual segmentation of the tumor outline in the planning software. Glioma volume was defined as the volume of increased intensity on T_1-weighted imaging with gadolinium. Tumor volume for non-enhanced tumors was defined as the area of increased intensity on T_2-weighted imaging. Subtotal or greater resection was defined as a postoperative finding of a >95% reduction in tumor volume.

Results

iMR imaging was performed 225 times during the 202 procedures. The period of interruption for each intraoperative MR imaging session was about 1 hour. The results of iMR imaging affected the surgical strategy in 33 of these 202 cases, including strategies for 25 of 73 gliomas (34%), 3 of 35 pituitary adenomas (8.6%), and 5 of 57 others. Additional removal after iMR imaging was performed in over 50% of cases of non-enhanced tumors and recurrent lesions. Gross total resection was achieved in 66% of 73 glioma cases (n = 48).

Volumetric analysis of primary supratentorial gliomas (n = 40) found that mean initial tumor volumes were 54.9 cm^3 (range 1.2–160.0 cm^3) in

Table 1 Summary of volumetric analysis in primary supratentorial gliomas

	LGG	HGG	All	HGG by Sanai et al.[9]
Number of patients	7	33	40	500
Gd enhancement (+/−)	2/5	29/4	31/9	—
Tumor volume (cm^3)*	18.3 (1.0–49.0)	54.9 (1.2–160.0)	48.4 (1.0–160.0)	65.8 (0.3–476.1)
Additional removal (+)	2 (33%)	9 (27%)	11 (32%)	—
Additional removal volume (cm^3)*	3.9 (0.4–7.3)	2.4 (0.3–8.0)	2.6 (0.3–8.0)	—
Residual tumor volume (cm^3)*	4.6 (6.5–12.7)	2.3 (0.8–25.5)	2.6 (0.8–25.5)	2.3 (0–80)
Intraoperative resection rate*	80.5% (40.7–100)	93.5% (34.5–100)	91.7% (34.5–100)	—
Resection rate*	83.2% (40.7–100)	95.1% (34.5–100)	93.5% (34.5–100)	96% (10–100)

*Values are mean (range). Gd: gadolinium, HGG: high-grade glioma, LGG: low-grade glioma.

high-grade glioma (HGG) and 18.3 cm^3 (range 1.0–49.0 cm^3) in low-grade glioma (LGG). The volume of additional removal after iMR imaging was 2.4 cm^3 (range 0.3–8.0 cm^3) in HGG and 3.9 cm^3 (range 0.4–7.3 cm^3) in LGG. Residual tumor volume was 2.3 cm^3 (range 0.8–25.5 cm^3) in HGG and 4.6 cm^3 (range 6.5–12.7 cm^3) in LGG. The EOR was 95.1% in HGG and 83.2% in LGG (Table 1). In addition, iMR imaging revealed an unexpected brain event in 1 patient (acute subdural hematoma). To evaluate the impact of iMR imaging, we analyzed the relationship between supratentorial glioma surgical staging (Table 2) and the incidence of additional removal after iMR imaging. This surgical staging was proposed by Nomura and Kayama and the Japanese Brain Tumor group in 2004.[5] We analyzed 44 cases of primary supratentorial glioma (4 cases were added following the volumetric analysis): stage 1, n = 0; stage 2, n = 5; stage 3, n = 21; stage 4, n = 12; stage 5, n = 6. No additional removal was performed for cases in stages 1, 2, or 5. Additional removal after iMR imaging achieved subtotal resection in 3 cases (14%) in stage 3 and 3 cases (25%) in stage 4 (Fig. 2).

MEP monitoring was combined with iMR imaging in 32 gliomas. MEP monitoring was successful in 30 cases (94%), and was only unsuccessful in 2 patients with preoperative severe motor weakness. Table 3 shows the results of MEP monitoring and postoperative motor function. Preoperative motor deficits were improved in 4 patients and remained unchanged in 19 patients. Permanent motor deficits were identified in 5 patients, 2 patients with decreased amplitude of MEP and 3 patients with no changes in MEP amplitude. Transient decreases in MEP amplitude were seen in 2 patients. One of these two patients had left temporal glioblastoma and showed transient decreases in MEP amplitude caused by middle cerebral artery compression (Fig. 3). iMR imaging showed no ischemic changes, but diffusion-weighted imaging after surgery clearly showed an ischemic lesion around the left internal capsule.

Table 2 Surgical staging for glioma

Stage	Definition
1	tumor size ≤1 cm or within one gyrus
2	Stage 1 (+1) or tumor size >1 cm to <3 cm
3	Stage 2 (+1) or tumor size >3 cm
4	Stage 3 (+1) or stage 2 (+1+1)
5	Stage 3 (+1+1) or stage 2 (+1+1+1) or multiple lesions, disseminated lesions, extra-CNS lesions

+1: Eloquent area (motor, speech, visual); thalamus, basal ganglia, bilateral lesions; sylvian fissure (insular cortex). CNS: central nervous system. Reproduced with permission from Kayama et al.: [A proposed staging system for glioma surgery]. *No Shinkei Geka Journal* 13: 448–453, 2004 (Japanese),[5] ©2004, The Japanese Congress of Neurological Surgeons.

Discussion

The present study suggests that the best use for iMR imaging and integrated navigation seems to be for glioma surgery. In our series, 34% of glioma cases

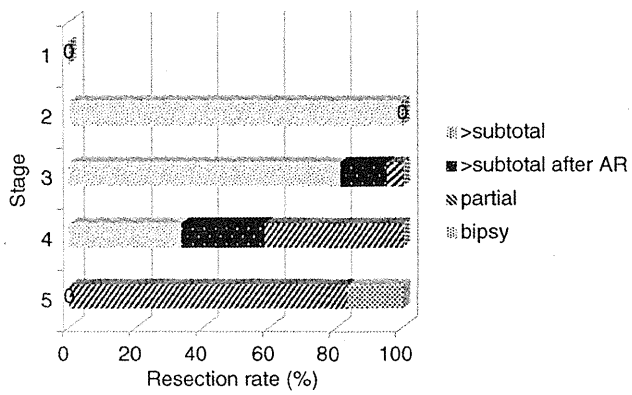

Fig. 2 Surgical staging and resection rate. Tumors in stages 1, 2, and 5 underwent no additional removal (AR) after intraoperative magnetic resonance imaging. AR was performed for 14% of stage 3 cases and 25% of stage 4 cases.

Table 3 Results of intraoperative motor evoked potential (MEP) monitoring and postoperative motor function

MEP	Postoperative motor function				Total
	Improve	No change	Transient aggravation	Permanent aggravation	
No change	3	19	1	3	26
Transient decrease in amplitude	1	0	1	0	2
Permanent decrease in amplitude (<50%)	0	0	0	2	2
Total	4	19	2	5	30

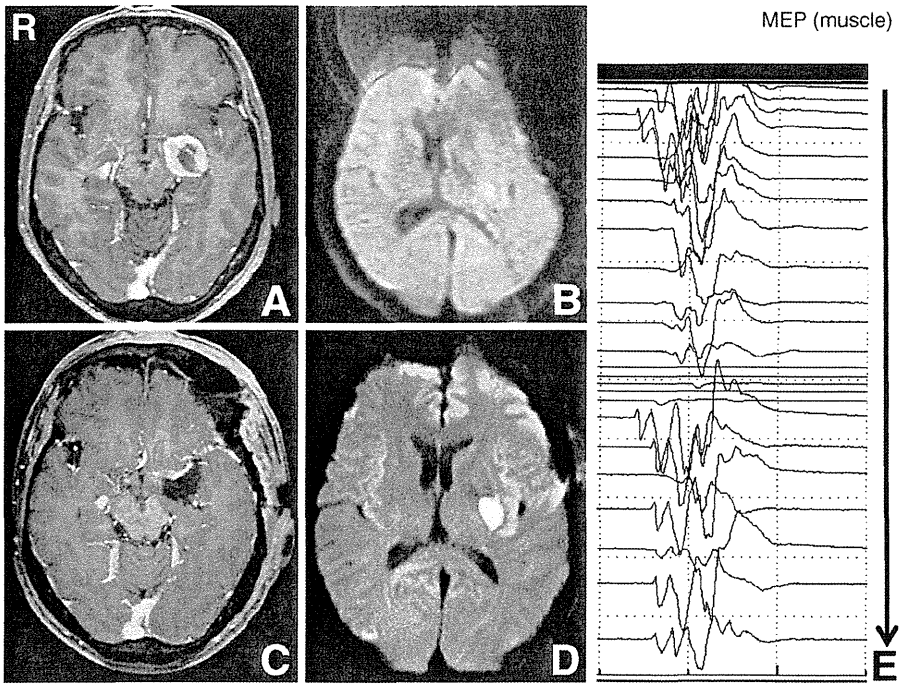

Fig. 3 Representative case of left temporal glioblastoma showing transient decrease in motor evoked potential (MEP) amplitude. A: Preoperative T_1-weighted magnetic resonance (MR) image with gadolinium. B: Intraoperative diffusion-weighted MR image. C: Postoperative T_1-weighted MR image with gadolinium. D: Postoperative diffusion-weighted MR image. E: Temporal changes in response of the thenar muscles. Transient decrease in amplitude occurred during middle cerebral artery compression, but recovered after releasing the compression.

were improved and the EOR was increased following iMR imaging. This modality offers particularly important contributions to modification of surgery in non-enhanced and recurrent tumors. In addition, iMR imaging is a good method to overcome technical problems encountered during surgery, such as unclear margins of microscopic and pathological findings and brain shift. In patients with newly diagnosed glioblastomas, increased EOR parallels improvements in overall survival, even at the highest levels of resection, and subtotal resections as low as 78% confer survival benefits.[9] Our results are similar to these findings (Table 1). In our series, the resection rate of LGG was lower than that of HGG. Three of 7 LGGs were located in eloquent areas, so we intentionally performed partial resection. The resection rates of these cases ranged from 40.7% to 71.9%. Safer resection could be performed for LGG than for HGG considering the long natural history of LGG. Randomized controlled trials of iMR imaging-guided glioma surgery did not demonstrate survival benefits.[10] However, iMR imaging guidance in glioma surgery did help surgeons achieve the optimum EOR.

This study analyzed surgical staging and additional (modified) removal after iMR imaging. For tumors classified in stages 1, 2, or 5, no modification was required after iMR imaging. Stage 5 tumors are not resectable to ensure preservation of brain function. In contrast, tumors in stages 3 and 4 underwent the modification after iMR imaging in 15–25% of cases. Moreover, over 50% of recurrent or non-enhanced tumors underwent modification after iMR imaging. iMR imaging is mainly useful for safety management in patients with stage 1, 2, or 5 lesions. Safety management is one of the important purposes of iMR imaging. In our series, we were able to detect left acute subdural hemorrhage during right temporal glioblastoma removal,[7] and could remove the hematoma immediately after tumor resection. The postoperative course was uneventful and the patient remained alive as of 26 months postoperatively.

Review of iMR imaging-guided resection of glioblastoma pointed out the limitations in the available literature,[6] and also suggested cost as an important outcome parameter. Our Surgical Suite® has separate components in the operating room and MR imaging room. Consequently, the system can be used not only for intraoperative imaging, but also for pre- and postoperative imaging and brain checks for inpatients. We have also tried to use iMR imaging in various neurosurgical operations. T_1-weight-

ed imaging with gadolinium clearly shows residual tumor in the pituitary region, and intraoperative time-resolved contrast-kinetics imaging can reveal complete resection of arteriovenous malformation without the need for conventional catheter angiography.[8]

The present study examined the associations between MEP monitoring and postoperative motor function in 32 patients. MEP monitoring was successful in 30 patients (94%), excluding 2 patients with severe preoperative motor weakness. Preoperative motor deficits recovered in 4 patients, whereas 19 patients showed no changes in motor function. Permanent deficits occurred in 5 patients. We were able to detect decreases in amplitude for 2 patients, but the remaining 3 patients did not show any change in MEP amplitude during surgery. One patient with precentral gyrus glioblastoma suffered motor weakness of the upper limb, and one patient had frontal gliosarcoma. We temporarily clipped the feeding arteries, and checked MEP responses within 20–30 minutes during gliosarcoma removal. We confirmed that MEP responses were unchanged, and then cut the feeder vessels. Postoperative MR imaging revealed an ischemic lesion, including the pyramidal tract. We speculate that the blood supply to the pyramidal tract during surgery was sufficient, but was altered by leptomeningeal anastomosis after surgery. Figure 3 shows the usefulness of MEP monitoring. Compression of the middle cerebral artery caused decrease in MEP amplitude. We were able to prevent permanent deficits based on the warnings provided by MEP monitoring. MEP monitoring is an essential tool for preserving motor function in patients with glioma near the motor cortex or pyramidal tract. We have safely performed 6 awake craniotomies with the use of this iMR imaging system. Combining MEP monitoring with awake craniotomy and iMR imaging appears to offer the most effective method for safe glioma surgery near eloquent areas. Further study of the impact of an iMR imaging system on surgical success and patient survival within the context of a large, prospective, population-based project is needed to confirm the present findings.

The present study shows that iMR imaging provides useful information that allows intraoperative modification of the surgical strategy, and MEP monitoring provides useful information for preserving motor function in patients with gliomas near the primary motor cortex and pyramidal tract. Combined use of iMR imaging, neuronavigation, and MEP monitoring offers the optimal tool for treating brain tumors around the motor cortex or pyramidal tract. This approach could be very helpful for maximizing resection and minimizing morbidity.

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CLINICAL STUDY

Treatment outcomes in glioblastoma patients aged 76 years or older: a multicenter retrospective cohort study

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Abstract Age is one of the most important prognostic factors in glioblastoma patients, but no standard treatment has been established for elderly patients with this condition. We therefore conducted a retrospective cohort study to evaluate treatment regimens and outcomes in elderly glioblastoma patients. The study population consisted of 79 glioblastoma patients aged ≥76 years (median age 78.0 years; 34 men and 45 women). The median preoperative Karnofsky performance status (KPS) score was 60. Surgical procedures were classified as biopsy (31 patients, 39.2 %), <95 % resection of the tumor (21 patients, 26.9 %), and ≥95 % resection of the tumor (26 patients, 33.3 %). Sixty-seven patients (81.0 %) received radiotherapy and 45 patients (57.0 %) received chemotherapy. The median overall progression-free survival time was 6.8 months, and the median overall survival time was 9.8 months. Patients aged ≥78 years were significantly less likely to receive radiotherapy ($p = 0.004$). Patients with a postoperative KPS score of ≥60 were significantly more likely to receive maintenance chemotherapy ($p = 0.008$). Multivariate analyses identified two independent prognostic factors: postoperative KPS score ≥60 (hazard ratio [HR] = 0.531, 95 % confidence interval [CI] 0.315–0.894, $p = 0.017$) and temozolomide therapy (HR = 0.442, 95 % CI 0.25–0.784, $p < 0.001$).The findings of this study suggest that postoperative KPS score is an important prognostic factor for glioblastoma patients aged ≥76 years, and that these patients may benefit from temozolomide therapy.

Keywords Glioblastoma · Karnofsky performance status score · Elderly patients · Temozolomide

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Introduction

Previous studies have reported several prognostic factors for glioblastoma including age, performance status (PS), the extent of tumor resection, and biological markers, with age being one of the most important factors [1].

Stupp et al. [2] conducted a phase III randomized clinical trial of 573 glioblastoma patients aged 18–70 years with World Health Organization PS 0–2, and reported a median overall survival (mOS) of 12.1 months in the group who received radiotherapy alone and 14.6 months in the group who received both radiotherapy and temozolomide (TMZ). On the basis of these results, the standard treatment for glioblastoma is a combination of surgical resection, radiotherapy, and chemotherapy with TMZ. However, the trial by Stupp et al. [2] included only patients aged ≤70 years. Several other important clinical trials also excluded elderly patients, and no standard treatment has been established for this group.

Some prospective studies have reported the use of TMZ in older patients with glioblastoma. Brandes et al. [3] conducted a prospective trial in elderly glioblastoma patients that included three treatment arms: (1) standard radiotherapy, (2) standard radiotherapy plus adjuvant procarbazine, lomustine, and vincristine (PCV), and (3) standard radiotherapy plus adjuvant TMZ. Patients in the TMZ group showed significantly increased OS compared with those treated with radiotherapy alone (14.9 vs. 11.2 months). In multivariate analysis, only the Karnofsky performance status (KPS) score was a significant factor associated with OS, and the association of TMZ was not significant. Pérez-Larraya el al. [4] reported a nonrandomized, phase II trial for patients ≥70 years old with a postoperative KPS score of <70. These patients were treated with TMZ without radiotherapy, and benefits were seen for TMZ alone in comparison with historical controls.

There is no clear definition of 'elderly' in this patient group, although many studies have defined elderly as ≥60 years or ≥65 years. The mean age of onset of glioblastoma is in the 60 s. Because of the aging population, the proportion of glioblastoma patients who are in the elderly age group is increasing. One report stated that the number of glioblastoma patients aged ≥65 years is expected to double from 2,000 to 2,030 [5].

One approach to developing treatment standards for elderly patients is to investigate glioblastoma in a group of more advanced age. A population-based study of 2,882 glioblastoma patients in Norway found that 15.9 % were aged ≥75 years [6]. Data from the Brain Tumor Registry of Japan (1984–2000) showed that 10.0 % of glioblastoma patients were aged ≥75 years [7]. This group is referred to as "late-stage elderly" in Japan. Only one previous study by Piccirilli et al. [8] has reported treatment outcomes in elderly late-stage glioblastoma patients.

We conducted a retrospective cohort study of glioblastoma patients aged ≥76 years who were treated at seven institutions in the Tohoku Brain Tumor Study Group, to evaluate treatment regimens and outcomes. We also aimed to elucidate problems specific to glioblastoma patients in this age group, and factors affecting the prognosis of these patients.

Methods

This study included patients aged ≥76 years with primary glioblastoma who were treated at seven institutions participating in the Tohoku Brain Tumor Study Group between January 1995 and January 2010. The diagnosis of glioblastoma was confirmed by histopathological examination in all patients.

Questionnaire survey forms were sent to each institution. Information collected in the survey was based on medical and surgical records, and head computed tomography (CT) or magnetic resonance imaging (MRI) findings. Factors surveyed included the number, location, and maximum diameter of tumors; preoperative and postoperative KPS scores; the extent of tumor resection; radiotherapy; chemotherapy (nimustine [ACNU] and ranimustine [MCNU]/TMZ); adverse reactions to chemotherapy; additional treatments; and preoperative and postoperative complications. Extent of resection was classified as biopsy if <50 % was resected, <95 % resection if 50–94 % of the tumor was resected, and ≥95 % resection if 95–100 % of the tumor was resected according to the assessment of the surgeon. Nine of the authors (T.U., K.A., T.S., K.S., T.K., T.B., M.I., C.K., and H.A.) then reviewed radiological images from all patients to determine the accuracy of tumor resection classification. Adverse reactions to chemotherapy were classified according to the Common Toxicity Criteria for Adverse Events (CTCAE) Version 3.0 of the National Cancer Institute.

Patients who did not undergo contrast-enhanced CT or MRI before surgery were excluded. If several contrast-enhanced lesions were detected but T2-weighted or fluid-attenuated inversion recovery MRI indicated continuity between these lesions, the tumor was considered to be solitary. The preoperative KPS score was defined as the lowest KPS score recorded between admission and initial surgery, and the postoperative KPS score was defined as the highest KPS score recorded between surgery and discharge. We chose to use the lowest KPS score for preoperative assessment in order to eliminate the effects of corticosteroid or osmotic diuretic drugs. For the postoperative KPS score, the highest records were considered to eliminate the effects of transient, postoperative neurological worsening.

The first day of treatment was defined as the day of surgery. Progression-free survival (PFS) was defined as the time to detection of tumor growth or death. Overall survival (OS) was defined as the time to the last confirmed survival date or death. Tumor growth was assessed using Macdonald's Criteria [9]. Age, maximum tumor diameter, and preoperative and postoperative KPS scores were compared between patients with values lower than the median and patients with values equal to or higher than the median.

Univariate analyses were performed using the Chi squared test and Mann–Whitney U-test. Survival curves were calculated using the Kaplan–Meier method and were compared using the log-rank test. Statistical significance was defined as a p value <0.05. Multivariate analyses of risk factors were performed using the Cox proportional hazards model. All analyses were performed using IBM SPSS statistics software, version 19.0 (IBM SPPS, Chicago, IL).

Results

Baseline characteristics of patients

Data from 80 patients were recorded, and 1 patient with inadequate preoperative images was excluded. Table 1 shows the baseline characteristics of the 79 patients included in the study. There were 34 men and 45 women, with a median age of 78.0 years (range 76–86 years). The preoperative KPS score ranged from 10 to 90 (median 60). The follow-up period ranged from 1.3 to 51.4 months (median 9.3 months). Seventy-five patients (94.9 %) died before the survey date. No patients died within 30 days after surgery.

The initial surgical procedure was biopsy in 31 patients (39.2 %) and tumor resection in 48 patients (60.8 %). One patient who underwent tumor resection did not undergo postoperative contrast-enhanced imaging and was excluded from the analysis of tumor resection. Twenty patients (25.3 %) underwent <95 % resection and 28 patients (35.4 %) underwent ≥95 % resection. Sixty-four patients (81.0 %) received radiotherapy, and 43 patients (54.4 %) received chemotherapy (12 patients received ACNU/MCNU and 25 patients received TMZ, and 6 patients received both ACNU and TMZ). All of the ACNU/MCNU-treated patients in this study were treated prior to the approval of TMZ in Japan in 2006. ACNU was administered as adjuvant chemotherapy followed by radiation for 2–4 (median 3) cycles to 2 patients. TMZ was also administered as adjuvant chemotherapy for 1–32 (median 6.5) cycles (150–200 mg/m^2 day, 5 days/4 weeks) to 27 patients.

Tumor recurrence was observed in 51 patients (64.6 %). Additional treatments for recurrence included stereotactic radiotherapy in five patients (6.3 %) and salvage surgery in three patients (3.8 %).

Treatment regimens according to age and KPS scores

Table 2 shows treatment regimens according to age and pre- and postoperative KPS scores. Patients aged ≥78 years were significantly less likely to receive radiotherapy ($p = 0.004$). Patients with a postoperative KPS score of ≥60 were significantly more likely to receive maintenance chemotherapy than patients with a postoperative KPS score of <60 ($p = 0.008$). Biopsy versus tumor resection was not significantly associated with age or preoperative KPS score.

Perioperative complications

Table 3 shows perioperative complications. The complications that occurred in five or more patients were analyzed using the log-rank test. Complications directly associated with surgery (worsening of hemiparesis, worsening of cognitive dysfunction, postoperative bleeding, and worsening of aphasia) were observed in 18 of the 79 patients (22.8 %). Patients with a previous stroke had a significantly shorter survival time ($p = 0.048$).

Univariate analyses of relationships between patient characteristics and survival

The median PFS (mPFS) was 6.8 months, and the median OS was 9.8 months (Fig. 1).

Tables 1 and 3 show the results of univariate analyses of the relationships between patient characteristics and mOS. The factors that were significantly associated with mOS were a postoperative KPS score of <60 or ≥60 (7.4 vs. 14.3 months, $p < 0.001$), previous stroke present or absent (5.9 vs. 10.2 months, $p = 0.048$), radiotherapy received or not received (11.8 vs. 5.3 months, $p = 0.001$), and TMZ received or not received (16.3 vs. 7.1 months, $p < 0.001$). There was no significant difference in mOS between patients with a preoperative KPS score of ≥60 or <60 (10.2 vs. 9.5 months, $p = 0.736$). Figure 1 shows Kaplan–Meier curves of estimated survival. Patients who underwent <95 % resection tended to have a shorter mOS than patients who underwent ≥95 % resection, but this difference was not significant (8.8 vs. 15.8 months, $p = 0.052$). Patients who underwent ≥95 % resection tended to have a longer mOS than those who underwent biopsy only, but this difference was also not significant (9.1 vs. 13.0 months, $p = 0.103$).

The median PFS was 4.6, 5.8, 10.0, and 17.9 months in the no-chemotherapy ($n = 36$), ACNU/MCNU-treated ($n = 12$), TMZ-treated ($n = 25$), and ACNU/MCNU plus TMZ-treated ($n = 6$) groups, respectively. There was no statistically significant difference between the ACNU/MCNU-treated and TMZ-treated groups ($p = 0.812$).

Table 1 Baseline patient characteristics and patient treatments, and the results of univariate analyses of the relationships between these factors and overall survival

Characteristic	No. of patients (%)	*p* value (log-rank test)
Gender		0.822
Male	34 (43.0)	
Female	45 (57.0)	
Age (years)		
Median	78	
Range	76–86	
≥78	55	0.504
<78	24	
Preoperative KPS score		
Median	60	
Range	10–90	
≥60	40	0.736
<60	39	
Postoperative KPS score		
Median	60	
Range	10–100	
≥60	44	<0.001*
<60	35	
Multicentric disease		0.87
No	71 (89.9)	
Yes	8 (10.1)	
Disease distribution		
Right	31 (39.2)	
Left	39 (49.4)	
Midline	2 (2.5)	
Bilateral	7 (8.9)	
Tumor location		
Frontal	33 (41.8)	
Temporal	11 (13.9)	
Parietal	22 (27.8)	
Occipital	3 (3.8)	
Basal ganglia	3 (3.8)	
Thalamus	2 (2.5)	
Corpus callosum	2 (2.5)	
Lateral ventricle	1 (1.3)	
Other	2 (2.5)	
Maximum tumor diameter (cm)		
Median	4.5	
Range	1.4–8.0	
≥4.5	40	0.107
<4.5	35	
Extent of surgery		0.052
Biopsy	31 (39.2)	
<95 % resection	21 (26.9)	
≥95 % resection	26 (33.3)	
Radiotherapy		0.001*
Yes	64 (81.0)	
59.4–61.6 Gy (30–35 fr)	42 (65.6)	
30–39 Gy (10–13 fr)	14 (21.9)	
52–54 Gy (26–27 fr)	3 (4.7)	
84 Gy (44 fr)	2 (3.1)	
15 Gy (brachytherapy)	2 (3.1)	
60 Gy (40 fr)	1 (1.6)	
Chemotherapy		
Yes	43 (54.4)	
TMZ therapy		<0.001*
Total	31	
Concomitant	19	
Adjuvant	27	
ACNU/MCNU therapy		0.84
Total	18	
Concomitant	16	
Adjuvant	3	
Myelosuppression (CTCAE grade ≥ 3)		
Concomitant ACNU/MCNU	5/16 (31.3)	
Concomitant TMZ	4/19 (3.7)	
Adjuvant ACNU/MCNU	1/3 (33.3)	
Adjuvant TMZ	1/27 (3.7)	
Adjuvant SRT/SRS	5 (6.3)	0.078
Second look surgery	3 (3.8)	
Recurrence		
Yes	51 (64.6)	
No	19 (24.1)	
Unknown	9 (11.4)	
Outcome		
Alive	4 (5.1)	
Dead	75 (94.9)	

* $p < 0.05$

Multivariate analyses using the Cox proportional hazards model

Table 4 shows the results of multivariate analyses of the relationships between mOS and postoperative KPS score (<60 or ≥60), radiotherapy (received or not received), TMZ (received or not received), and previous stroke (present or absent). Postoperative KPS score (hazard ratio [HR] = 0.531, 95 % confidence interval [CI] 0.315–0.894, $p = 0.017$) and TMZ therapy (HR = 0.442, 95 % CI 0.25–0.784, $p < 0.001$) were identified as independent prognostic factors.

Table 2 Treatment regimens according to age and KPS scores

	Age <78	Age ≥78	*p* value	Preoperative KPS <60	Preoperative KPS ≥60	*p* value	Postoperative KPS <60	Postoperative KPS ≥60	*p* value
Biopsy	7	24	0.317	14	17	0.647			
Resection	17	31		25	23				
Radiotherapy (+)	24	40	0.004*	31	33	0.781	26	38	0.249
Radiotherapy (–)	0	15		8	7		9	6	
Concomitant chemotherapy (+)	13	21	0.648	20	14	0.129	15	19	1.000
Concomitant chemotherapy (–)	9	34		18	25		20	23	
Adjuvant chemotherapy (+)	11	21	0.44	15	17	0.813	8	24	0.008*
Adjuvant chemotherapy (–)	10	30		21	19		23	17	

* $p < 0.05$

Table 3 Perioperative complications, and the results of univariate analyses of the relationships between these factors and overall survival

Complication	*n*	*p* value (log-rank test)
Preoperative complications		
Hypertension	28	0.778
Malignant tumor	10	0.417
Cognitive dysfunction	5	0.639
Chronic respiratory failure	5	0.271
Stroke	5	0.048*
Ischemic heart disease	4	
Arrhythmia	4	
Diabetes mellitus	2	
Chronic renal failure	2	
Liver dysfunction	2	
Postoperative complications		
Hemiparesis	13	0.096
Cognitive dysfunction	6	
Postoperative hemorrhage	2	
Aphasia	3	
Respiratory dysfunction	2	
Deep vein thrombosis	1	

* $p < 0.05$

Discussion

Among all 79 patients, mPFS was 6.8 months and mOS was 9.8 months. Even though the study included glioblastoma patients aged ≥76 years with a low PS, the outcomes were relatively favorable.

Age is one of the most important prognostic factors in glioblastoma patients [1]. The lack of standard treatment regimens for elderly glioblastoma patients may be one of the reasons why this group has a poor prognosis. These patients may be less likely to receive surgery, radiotherapy, and chemotherapy. Kita et al. [10] reported that the proportion of glioblastoma patients receiving only best supportive care increased with age, and that 75 % of patients aged ≥75 years received only best supportive care. Barnholtz-Sloan et al. [11] analyzed the treatment of 1,753 malignant glioma patients aged ≥66 years, and found that multidisciplinary treatment was significantly less common in patients aged ≥75 years.

Of the 79 patients in the present study, 48 (60.8 %) underwent surgical resection, 64 (81.0 %) received radiotherapy, and 45 (57.0 %) received chemotherapy. Data from the Brain Tumor Registry of Japan between 1984 and 2000 show that 3,695 of 5,328 patients (69.4 %) underwent tumor resection, 4,649 of 5,395 patients (86.2 %) received radiotherapy, and 3,403 of 4,985 patients (68.3 %) received chemotherapy [7]. All these treatment regimens were administered at a lower rate in our study group. Our findings show that more elderly patients were significantly less likely to receive radiotherapy, and that elderly patients with low a postoperative KPS score were significantly less likely to receive maintenance chemotherapy. Although biopsy versus surgical resection was not significantly associated with age or preoperative KPS score, we observed that radiological findings reflecting tumor location and extent of invasion might influence the choice of biopsy versus surgical resection. Scott et al. [12] conducted a retrospective study of 206 glioblastoma patients aged ≥70 years, and reported that 45 % of patients underwent surgical resection, 60 % received radiotherapy, and 20 % received chemotherapy, with a mOS of 4.5 months. In comparison, the patients in our study were more likely to receive radiotherapy and chemotherapy, which may have contributed to the longer survival times.